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DOCKET NO.: ALZA-0142 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
George V. Guittard, *et al.*
Application No.: 10/645,467
Filing Date: August 20, 2003
For: METHOD FOR MANAGEMENT OF INCONTINENCE

Confirmation No.: 8204
Group Art Unit: 1616
Examiner: George, Konata M.

CERTIFICATE OF FACSIMILE TRANSMISSION

DATE: August 21, 2006

I HEREBY CERTIFY THAT THIS PAPER IS BEING FACSIMILE TRANSMITTED TO THE PATENT AND TRADEMARK OFFICE TO FACSIMILE NUMBER 571-273-8300 ON THE DATE LISTED ABOVE.

Wendy A. Choi, Registration No. 36,697

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

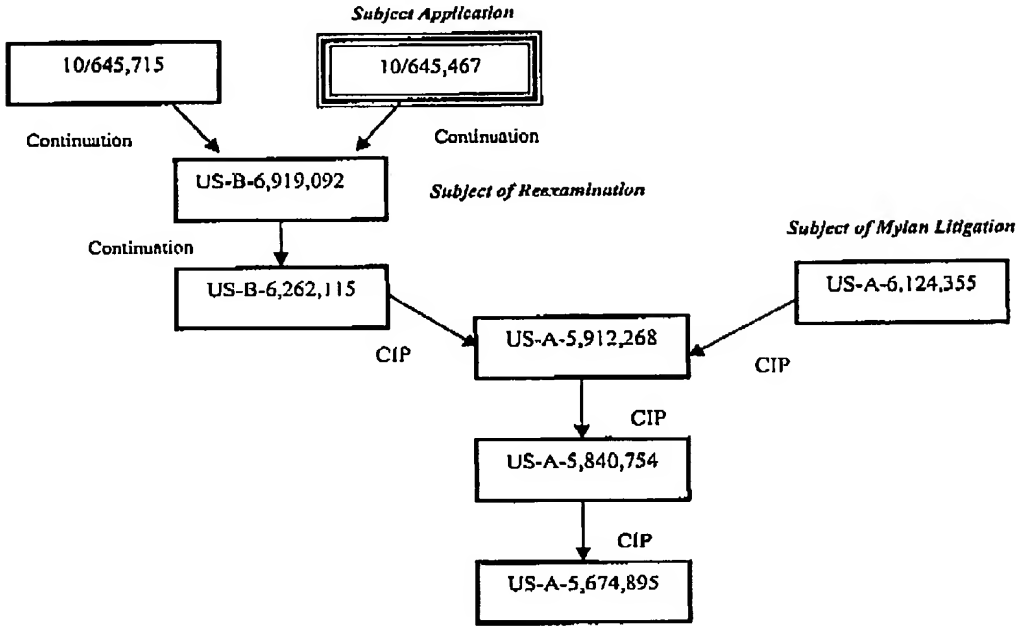
Dear Sir:

COMMUNICATION REGARDING STATUS OF RELATED APPLICATION

Pursuant to 37 CFR § 1.56 and in accordance with 37 CFR §§ 1.97-1.98, information relating to the above-identified application is hereby disclosed that may be helpful to the U.S. Patent and Trademark Office (PTO) in its consideration of the above-identified reexamination. Inclusion of information in this statement is not to be construed as an admission that this information is material as that term is defined in 37 CFR § 1.56(b).

ALZA Corporation, the assignee of this application, has filed a Request for Reexamination of claims 1 to 23 of related U.S. Patent No. 6,919,092 ("092 Patent"). This application is a continuation of Application No. 09/785,805, which issued as the 092 Patent. The reexamination of the 092 Patent was assigned to Examiner Evelyn Mei Huang, and has been granted. A final rejection has been issued in the reexamination of the 092 Patent.

Patentees are filing a response to the final rejection on even date with this Communication. A copy of the final rejection and the response are attached as Exhibit A and Exhibit B, respectively.



Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050. This form is submitted in duplicate.

Date: **August 21, 2006**

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Please deliver this and the following pages to:

Examiner:	**K. M. George**
U.S.P.T.O. Group Art Unit:	**1616**
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COVER MESSAGE:

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Attached hereto is/are the following documents:

1) Communication Regarding Status of Related Application
2) Exhibit A: Copy of Office Action Dated June 20, 2006
3) Exhibit B: Copy of Response Pursuant to 37 CFR 1.550(b)

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EXHIBIT A

United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/007,772	10/21/2005	6919092	ALZA-0141	3781

45511 7590 06/20/2006

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EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED: 06/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action in Ex Parte Reexamination	90/007,772	6918092	
	Examiner Evelyn Huang	Art Unit 3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

a☒ Responsive to the communication(s) filed on *07 April 2006*. b☒ This action is made FINAL.
c☐ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire 2 month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).** If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☒ Information Disclosure Statement, PTO-1449.
3. ☐ Interview Summary, PTO-474.
4. ☐ _____.

Part II SUMMARY OF ACTION

1a. ☒ Claims *2-23* are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☒ Claims *1* have been canceled in the present reexamination proceeding.
3. ☐ Claims _____ are patentable and/or confirmed.
4. ☒ Claims *2-23* are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ The drawings, filed on _____ are acceptable.
7. ☐ The proposed drawing correction, filed on _____ has been (7a)☐ approved (7b)☐ disapproved.
8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
   a)☐ All b)☐ Some* c)☐ None of the certified copies have
   1☐ been received.
   2☐ not been received.
   3☐ been filed in Application No. _____.
   4☐ been filed in reexamination Control No. _____.
   5☐ been received by the International Bureau in PCT application No. _____.
   * See the attached detailed Office action for a list of the certified copies not received.
9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.
10. ☐ Other: _____

cc: Requester (if third party requester)

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Reexamination

1. This is the final office action in the reexamination proceeding of U.S. Patent No. 6,919,092 issued on 7-19-2005 to Guittard.

Procedural Posture

2. The request by the Requester (Patent Owner) for ex parte reexamination was filed on 10-21-2005.

The wavier of the Patent Owner's Statement was filed on 1-10-2006.

The response to the non-final office action mailed on 2/7/2006 was filed on 4/7/2006.

Status of the Claims

3. In the amendment filed on 4/7/2006, claim 1 has been cancelled.

Currently, claims 2-23 are pending.

Improper Amendment

4. The amendment filed on 4/7/2006 fails to comply with 37 CFR 1.530 as follows:

the amendment does not comply with 37 CFR 1.530 (e) because it fails to supply the status (i.e. *pending* or canceled), as of the date of the amendment, of ***all*** patent claims.

In order to prevent any further delay of the reexamination proceeding and to ensure that it is conducted with special dispatch, the Office has *sua sponte* waived the requirements of 37 CFR 1.530 (e), to the extent that the improper amendment of 4/7/2006 is accepted. This waiver is based solely on the present facts and circumstances, and is not to be taken as guidance as to any future waiver of the rules. Senior Legal Advisor Kenneth M. Schor has signed this action below solely for that purpose.

Future Amendment

5. Patent owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37CFR 1.20(c).

Submissions after this final action will be governed by the requirements of 37 CFR 1.116, which will be strictly enforced.

Ongoing Duty to disclose

6. The submission of the 41 pages PTO-1449 on 4/7/2006 is acknowledged.

Consideration by the examiner of the information submitted in an IDS means nothing more than considering the documents in the same manner as other documents in Office search

files are considered by the examiner while conducting a search of the prior art in a proper field of search. See MPEP 609, at page 600-125. The initials of the examiner placed adjacent to the citations on the PTO-1449, or PTO/SB/08A and 08B, or its equivalent mean that the information has been considered by the examiner to the extent noted above.

7. The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a), to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 6,919,092 throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Priority

8. The reexamination patent is a continuation of application No. 09/280,309, filed on 3-29-1999, now US Pat. No. 6,262,115, which is a CIP of application No. 08/806,773, filed on 2-26-1997, now US Pat. No. 5,912,268, which is a CIP of application No. 08/706,576, filed on 9-5-1996, now US Pat. No. 5,840,754, which is a CIP of application No. 08/445,849, filed on 5-22-1995, now US Pat. No. 5, 674,895.

9. For claims 3-23, the maximum plasma oxybutynin concentration of 'about 0.28 ng/ml to about 0.45 ng/ml per mg' of oxybutynin or its pharmaceutically acceptable salt was described for the first time in application No. 08/706,576, filed on 9-5-1996, now US Pat. No. 5,840,754 (column 10, lines 55-65). Accordingly, the earliest effective filing date for claims 3-23 would be 9-5-1996.

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10. The description for Claim 2 is found in application No. 08/445,849, filed on 5-22-1995, now US Pat. No. 5, 674,895. Accordingly, the earliest effective filing date for claim 2 would be 5-22-1995.

Withdrawn Claim Rejections - 35 USC § 102(b)

11. The rejection for Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Guittard I (US 5,674,895, issued on 10-7-1997) is rendered moot by the cancellation of claim 1.

12. The rejection for Claim under 35 U.S.C. 102(b) as being anticipated by Guittard II (WO 96/37202, published on 11-28-1996) is rendered moot by the cancellation of claim 1.

13. The rejection for Claim 1 under 35 U.S.C. 102(b) as being anticipated by Rantala (WO 96/12477, published on 5-2-1996) is rendered moot by the cancellation of claim 1.

14. The rejection for Claim 1 under 35 U.S.C. 102(b) as being anticipated by Baichwal (US 5,399,359, issued on 3-21-1995) is rendered moot by the cancellation of claim 1.

Withdrawn Claim Rejections - 35 USC § 103(a)

15. The rejection for claim 1 under 35 U.S.C. 103(a) as being unpatentable over Wong (US 5,082,668) and PDR (42nd edition, 1988, pages 1222-3, Immediate release Ditropan) and Robinson (Prescriber's Journal, 34(1):27-30, 1994) is rendered moot by the cancellation of claim 1.

16. The rejection for claim 1 under 35 U.S.C. 103(a) as being unpatentable over Morella (US 5,330,766)) and Robinson (Prescriber's Journal, 34(1):27-30, 1994 is rendered moot by the cancellation of claim 1.

Withdrawn Double Patenting Rejection

17. The rejection for Claim 1 under 35 U.S.C. 101 as claiming the same invention as that of claim 1 of prior U.S. Patent No. 6,262,115 is withdrawn in view of the cancellation of claim 1.

Outstanding Claim Rejections - 35 USC § 102(a)

18. ***The rejection for Claim 2 under 35 U.S.C. 102(a) as being anticipated by Baichwal (US 5,399,359) is maintained for reasons of record.***

Claim 2 has been amended to incorporate 'for treating incontinence in a patient' into the claim. In view of the amendment, the rejection is restated as follows.

Instant Claim 2 is directed to a pharmaceutical dosage form comprising 240 ng to 650 mg of a member selected from oxybutynin and its pharmaceutically acceptable salt, that releases the member at a controlled and sustained, substantially zero order rate for about 24 hours, for treating incontinence in a patient.

Baichwal's once-a-day tablet (column 7, Example 3) comprising 10 mg oxybutynin hydrochloride (2.9% of 348.3 mg tablet weight) with a controlled and sustained, substantially zero order release profile as described in Table 6 (column 8) for the relief of symptoms of bladder instability associated with voiding of the bladder (i.e. management of incontinence in a patient) (column 2, line 67 to column 3, line 1) meets all the requirements of claim 2.

Outstanding Claim Rejections - 35 USC § 102(e)

19. The rejection for Claim 2 under 35 U.S.C. 102(e) as being anticipated by Baichwal (US 5,399,359) is maintained for reasons of record.

Claim 2 has been amended to incorporate 'for treating incontinence in a patient' into the claim. In view of the amendment, the rejection is restated as follows.

Instant Claim 2 is directed to a pharmaceutical dosage form comprising 240 ng to 650 mg of a member selected from oxybutynin and its pharmaceutically acceptable salt, that releases the member at a controlled and sustained, substantially zero order rate for about 24 hours for treating incontinence in a patient.

Baichwal's once-a-day tablet (column 7, Example 3) comprising 10 mg oxybutynin hydrochloride (2.9% of 348.3 mg tablet weight) with a controlled and sustained, substantially zero order release profile as described in Table 6 (column 8) for the relief of symptoms of bladder instability associated with voiding of the bladder (i.e. management of incontinence in a patient) (column 2, line 67 to column 3, line 1) meets all the requirements of claim 2.

Response to Arguments

20. *Patentee submits that the release of drug according to Example 3 of Baichwal does not produce a linear plot, much less a plot reflecting the claimed zero order release rate. Furthermore, it appears that the vast majority of oxybutynin in Baichwal's examples is released in 12 hours or less. That Example 3 of Baichwal may occasionally produce results that fall within claim 2 would be insufficient to establish anticipation.*

The mere assertion that Baichwal's Example 3 does not produce a linear plot of release of drug vs. time without any showing of evidence is insufficient to overcome the anticipation rejection. The arguments of counsel cannot take the place of evidence in the record. *In re Schulze* 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965).

Furthermore, even if the plot of Baichwal's Example 3 is not exactly linear, it would still be embraced by the instant claim which only require a '***substantially*** zero order release rate'.

The statement that the other examples described by Baichwal do not meet the requirements of instant claim is irrelevant, since this anticipation rejection is based on the sustained release formulation of Example 3, which provides controlled release of oxybutynin for

24 hours with a substantially zero order release kinetics and fully meets the requirement of instant claim 2.

Patentee further submits that Example 3 may only occasionally produce results that falls within claim 2, implicating that the data of Example 3 is not always reproducible. However, a US patent is presumed to be valid in the absence of evidence to the contrary. MPEP 2121.

In conclusion, claim 2 is clearly anticipated by Baichwal's once-a-day tablet (column 7, Example 3) comprising 10 mg oxybutynin hydrochloride with a controlled and sustained, substantially zero order release profile as described in Table 6 (column 8).

Outstanding Claim Rejections - 35 USC § 102((b)

21. ***The rejection for Claims 3-23 under 35 U.S.C. 102(b) as being anticipated by, or in the alternative obvious, over Baichwal (US 5,399,359, issued on 3-21-1995) in view of Lukkari (Clinical pharmacology of oxybutynin, with special reference to pharmacokinetics and interactions. University of Helsinki, Finland, 1997) and Doctor's Guide with translated package insert (Cystrin CR launched in Finland for urinary incontinence. May 7, 1998) is maintained for reasons of record.***

Claim 3 has been amended to incorporate 'for treating incontinence in a patient' into the claim. In view of the amendment, the rejection is restated as follows.

Instant claim 3 is directed to a dosage form comprising 5 mg to 250 mg of a member selected from oxybutynin and its pharmaceutically acceptable salt, wherein (i) said dosage provides a maximum plasma oxybutynin concentration of about 0.28 ng/ml to about 0.45 ng/ml per mg of said member in said dosage form and (ii) wherein said member is delivered from said dosage form over a period of about 24 hours for treating incontinence in a patient.

Baichwal's once-a-day tablet (column 7, Example 3) comprising 10 mg oxybutynin hydrochloride (2.9% of 348.3 mg tablet weight) with a controlled and sustained, substantially zero order release profile as described in Table 6 (column 8) is for the relief of symptoms of bladder instability associated with voiding of the bladder (i.e. management of incontinence in a patient) (column 2, line 67 to column 3, line 1). Baichwal's tablet has been marketed as ***Cystrin CR*** for treatment of incontinence (***Doctor's Guide***). The maximum plasma oxybutynin hydrochloride concentration (C_{max}) in patients who have ingested Cystrin CR has been determined to be 0.28 ng/ml (under fasting condition, or 1 hour before breakfast) and 0.43 ng/ml per mg oxybutynin hydrochloride (2 hours after breakfast) (***Lukkari***, page 31, Table 2, Study IV and Study V). Baichwal's tablet formulation of Example 3 therefore meets all the requirements of instant claim 3.

Baichwal's tablet formulation of Example 3 also meet the limitations of instant ***claim 4*** (which requires the salt in claim 3 be oxybutynin hydrochloride), ***claims 5 and 8*** (which require the dosage form of claims 4 and 3 respectively delivers at a substantially zero order rate of release) and ***claims 9-12*** (which require the dosage form of claims 3, 4, 6, 7 respectively to be a tablet).

Baichwal further teaches that the dosage form may be coated with a hydrophilic coating, such as hydroxypropylmethylcellulose (column 5, lines 58-62) as required by instant ***claims 6 and 7.***

For instant ***claims 13-22***, directed to a method for the management of incontinence in a patient, comprising administering to the patient a dosage form corresponding to the composition claims 3-12, Baichwal's method (column 2, line 67 to column 3, line 1) for the relief of symptoms of bladder instability associated with voiding of the bladder (i.e. management of incontinence in a patient) with the tablet formulation of Example 3 therefore meets all the requirements of these claims. Administering Baichwal's tablet of Example 3 to a patient would necessarily reduce the incidence of side effects associated with oxybutynin treatment as required by instant ***claim 23***.

Response to Arguments

22. *Patentee contends that Baichwal does not disclose administration of the oxybutynin dosage form under fasting conditions, one hour before breakfast or two hours after breakfast as described in Lukkari. Baichwal therefore fails to anticipate as the extrinsic evidence does not 'make clear that the missing descriptive matter is necessarily present in the thing described in the reference'. Furthermore, even if administering Baichwal's dosage form will occasionally result in the claimed maximum plasma concentration, it is insufficient to establish anticipation. MEHL/Biophile Inern. Corp. v. Milgraum, 192 F.3d 1362, 1365(Fed. Cir.1999).*

Patentee cites *MEHL* and argues that Baichwal does not provide the critical teaching of administering oxybutynin under fed or fasted state. Unlike *MEHL* where the prior art does not disclose the limitation of the claims, 'the fed or fasted state' is not a limitation in the instant claims. Accordingly, Baichwal needs not expressly disclose the fed or fasted state under which

the drug is administered to anticipate because the instant claims do not recite these administration conditions.

Contrary to Patentee's assertion that Baichwal's dosage form only occasionally result in the claimed maximum plasma concentration, Baichwal's oxybutynin dosage form administered in the fasted state invariably results in the maximum plasma concentration of about 0.28 ng/ml to about 0.45 ng/ml per mg of oxybutynin as required by the instant claim. The dosage form administered in the fasted state meeting all the requirements of the instant claim is equivalent to a species falling within the claimed genus, thereby anticipating the genus of instant claim 2. MPEP 2131.02.

Outstanding Claim Rejections - 35 USC § 102(a)

23. The rejection for Claims 3-5, 8-10, 13-14, 16, 18-20, 23 under 35 U.S.C. 102(a) as being anticipated by Rantala (WO 96/12477, published on 5-2-1996) is maintained for reasons of record.

Claim 3 has been amended to incorporate 'for treating incontinence in a patient' into the claim. The amendment does not overcome the rejection because the added intended use fails to set a demarcation from the prior art composition. The rejection is restated as follows.

Instant claim 3 is directed to a dosage form comprising 5 mg to 250 mg of a member selected from oxybutynin and its pharmaceutically acceptable salt, wherein (i) said dosage provides a maximum plasma oxybutynin concentration of about 0.28 ng/ml to about 0.45 ng/ml

per mg of said member in said dosage form and (ii) wherein said member is delivered from said dosage form over a period of about 24 hours for treating incontinence in a patient.

Rantala's tablet (page 9, Table 4, Example 3) comprises 10 mg oxybutynin hydrochloride (2.9% of 348.3 mg tablet weight) and has a controlled and sustained, substantially zero order release profile as indicated by the substantially constant plasma concentration over a 24 hour period (Fig. 1). Rantala's tablet is for the relief of symptoms of bladder instability associated with voiding of the bladder (i.e. management of incontinence in a patient) (page 1, lines 17 to 26). The maximum plasma oxybutynin hydrochloride concentration (C_{max}) has been determined to be 0.213 ng/ml, which is '***about*** 0.28 ng/ml per mg oxybutynin hydrochloride' as recited in instant claim 3. Rantala's Example 3 therefore meets all the requirements of instant ***claim 3.***

Rantala's tablet formulation of Example 3 also meet the limitations of instant ***claims 4*** (which requires the salt in claim 3 be oxybutynin hydrochloride), ***claims 5 and 8*** (which require the dosage form of claims 4 and 3 respectively delivers at a substantially zero order rate of release) and claims 9-10 (which require the dosage form of claims 3, 4 respectively to be a tablet).

Instant claims 13-14, 16, 18-20 are directed to a method for the management of incontinence in a patient, comprising administering to the patient a dosage form corresponding to the composition claims 3-5, 8-10.

Rantala's method (page 1, lines 17 to 26) for the relief of symptoms of bladder instability associated with voiding of the bladder (i.e. management of incontinence in a patient) with the tablet formulation of Example 3 therefore meets all the requirements of instant ***claims 13-14, 16, 18-20.***

Rantala further teaches that the controlled release tablet formulation (such as Example 3) has diminished anticholinergic side effects of oxybutynin (page 12, lines 33-37) as required by instant ***claim 23***.

Response to Arguments

24. *Patentee submits that the examiner fails to identify any evidence supporting its apparent conclusion that those skilled in the art would deem 0.213 ng/ml/mg to be 'about 0.28 ng/ml/mg' in spite of the fact that they differ by nearly 24%.*

A claim is to be given the broadest possible meaning consistent with the specification during the reexam proceeding. MPEP 2111. Accordingly, since a definition of 'about' and the statistical data on the variation of the maximum plasma concentration are not described in the specification, one of ordinary skill in the art would consider '0.213 ng/ml/mg' to be '***about*** 0.28 ng/ml/mg'.

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Outstanding Claim Rejections - 35 USC § 103

25. The rejection for Claim 2 under 35 U.S.C. 103(a) as being unpatentable over Wong (US 5,082,668) and PDR (42nd edition, 1988, pages 1222-3, Immediate release Ditropan) and Robinson (Prescriber's Journal, 34(1):27-30, 1994) is maintained for reasons of record.

Claim 2 has been amended to incorporate 'for treating incontinence in a patient' into the claim. The amendment does not overcome the rejection because the added intended use fails to set a demarcation from the prior art composition. In view of the amendment, the rejection is restated as follows.

Claim 2 is directed to a pharmaceutical dosage form comprising 240 ng to 650 mg of a member selected from oxybutynin and its pharmaceutically acceptable salt, that releases the member at a controlled and sustained, substantially zero order rate for about 24 hours for treating incontinence in a patient.

Robinson teaches that oxybutynin is an antispasmodic, anticholinergic and antimuscarinic drug for treatment of incontinence (page 27 first paragraph; page 28, second paragraph). A total daily dosage of 10-15 mg oxybutynin hydrochloride and the side effects thereof are also described (page 29, 3rd and 5th paragraphs). The side effects of the immediate-release Ditropan (oxybutynin hydrochloride) for treating incontinence are also described in *Immediate-release DITROPAN*, (Physician's Desk Reference, 42nd edition 1988, page 1222-23). To reduce the anticholinergic side effects of oxybutynin, Robinson suggested the use of a modified release formulation (page 28, paragraph 3).

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Robinson does not specifically describe the formulation with controlled and sustained, substantially zero order release rate for about 24 hours as recited in the instant claim 2.

However, controlled sustained release system with constant pushing source has been known for use with a wide variety of drugs, including drugs that act on the cholinergic receptors, or smooth muscles (***Wong***, column 20, lines 1-2). The osmotic pump dosage form of Wong has a zero order release rate over a period of about 24 hours (Fig. 11). Since oxybutynin is an antispasmodic, anticholinergic and antimuscarinic drug (Robinson, page 27), it would be embraced by Wong's controlled release formulation for drugs that act on the cholinergic receptors, or smooth muscles.

At the time of the invention, in view of the anticholinergic side effects of oxybutynin (Robinson, page 29, 3rd paragraph) and Wong's teaching that the controlled release drug delivery system would avoid patient compliance problems, uses less drug, minimizes side effects and thereby provides efficiency in treatment (column 4, lines 22-24), one of ordinary skill in the art would be motivated to formulate the oxybutynin hydrochloride into a controlled release delivery system as suggested by Robinson and specifically taught by Wong to arrive at a once-a-day oxybutynin hydrochloride formulation for the treatment of incontinence.

Response to Arguments

26. *Patentee contends that there is no motivation to combine Robinson with Wong. Robinson's disclosure of reducing anticholinergic side effects of oxybutynin through use of a modified release formulation is inconsistent with Wong's teaching of a dosage form for drugs*

intended to act upon cholinergic receptors. There is no reason for the skilled in the art to incorporate the drug with known side effects into a dosage form designed to achieve that side effect.

Wong teaches that the controlled release drug delivery system would avoid patient compliance problems, minimize the amount of drug used and the side effects thereof (column 4, lines 22-24), which is consistent with Robinson's teaching that the anticholinergic side effects of oxybutynin can be reduced by the use of a modified controlled release formulation (page 28). The active drugs for Wong's formulation are drugs that act upon 'cholinergic receptors, ...smooth muscles' (column 19, line 67 to column 20, line 2), i.e. anticholinergic/antimuscarinic drugs, including oxybutynin (Robinson, page 27). As it is well recognized in the art that predictable anticholinergic side effects come with anticholinergic drugs (Robinson, pages 27-28), the incorporation of an anticholinergic drug in Wong's dosage form is not 'designed' to achieve the anticholinergic side effects as Patentee asserted.

27. *Patentee argues that the skilled in the art would not be motivated to prepare the inventive once-a-day formulation because it is contrary to the conventional wisdom that orally ingested, controlled-release products had to release drug in 8-12 hours, before the product reached the colon, because of poor colon absorption (Gupta et al. page 268).*

While colonic drug absorption is believed to be poor and variable and may be of particular importance to once-a-day controlled release drug delivery systems, it has also been shown that some drugs are absorbed from the colon (Gupta, page 268, second paragraph). Accordingly, the fact that poor colonic drug absorption occurs for some drugs would not lead

one away from the preparation of the 24-hour controlled release formulation for oxybutynin, especially in view of the many advantages associated with such a formulation (Robinson, page 28; Wong column 4, lines 22-24) and the availability of the method for preparing such a formulation (Wong, column 1, lines 19-38).

Outstanding Claim Rejections - 35 USC § 103

28. ***The rejection for claim 2 under 35 U.S.C. 103(a) as being unpatentable over Morella (US 5,330,766)) and Robinson (Prescriber's Journal, 34(1):27-30, 1994) is maintained for reasons of record.***

Claim 2 has been amended to incorporate 'for treating incontinence in a patient' into the claim. In view of the amendment, the rejection is restated as follows.

Claim 2 is directed to a pharmaceutical dosage form comprising 240 ng to 650 mg of a member selected from oxybutynin and its pharmaceutically acceptable salt, that releases the member at a controlled and sustained, substantially zero order rate for about 24 hours for treating incontinence in a patient.

Robinson teaches that oxybutynin is an antispasmodic, anticholinergic and antimuscarinic drug for treatment of incontinence (page 27 first paragraph; page 28, second paragraph). A total daily dosage of 10-15 mg oxybutynin hydrochloride and the side effects thereof are also described (page 29, 3rd and 5th paragraphs). To reduce the anticholinergic side effects of oxybutynin, Robinson suggested the use of a modified release formulation (page 28, paragraph 3).

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Robinson does not specifically describe the formulation with controlled and sustained, substantially zero order release rate for about 24 hours as recited in the instant claim 2.

Morella, however, discloses a sustained release pharmaceutical composition and its preparation (column 23, claim 1) for a variety of drugs, including oxybutynin hydrochloride (column 5, line 32), which is known for treatment of incontinence. A substantially zero order rate release of the active drug over a 24 hour period is shown in Fig. 5 and described on column 16, Table 5.

Guided by the teachings of Morella and Robinson, one of ordinary skill in the art would be motivated to prepare the sustained release 10-15 mg oxybutynin hydrochloride formulation to reduce the anticholinergic side effects in the treatment of incontinence.

Response to Arguments

29. Patentee argues that the skilled in the art would not be motivated to prepare the inventive once-a-day formulation because it is contrary to the conventional wisdom that orally ingested, controlled-release products had to release drug in 8-12 hours, before the product reached the colon, because of poor colon absorption (Gupta et al. page 268).

While colonic drug absorption is believed to be poor and variable and may be of particular importance to once-a-day controlled release drug delivery systems, it has also been shown that some drugs are absorbed from the colon (Gupta, page 268, second paragraph).

Accordingly, the fact that poor colonic drug absorption occurs for some drugs would not lead one away from the preparation of the 24-hour controlled release formulation for oxybutynin, especially in view of the reduction of side effects associated with such a formulation (Robinson, page 28) and the availability of the method for preparing such a formulation (Morella, column 23, claim 1).

30. *Patentee submits that neither Morella nor Robinson discloses or suggests the claimed zero order release rate. Fig. 5 of Morella does not show a substantially zero order rate of release over 24 hours. Notably there are no data points between 600 minutes and 1440 minutes.*

The mere assertion that Morella's Fig. 5 does not show a substantially zero order release rate without any showing of evidence is insufficient to overcome the rejection. The arguments of counsel cannot take the place of evidence in the record. *In re Schulze* 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965).

Contrary to Patentee's assertion that Morella does not discloses or suggests the zero order release rate, Morella specifically defines 'sustained release' of his sustained release composition as 'release of active ingredient at such a rate that blood levels are maintained within the therapeutic range but below toxic levels over an extended period of time, e.g. 10-24 hours or greater' (column 2, lines 39-44). Morella further states that 'desirably the sustained release provides a generally constant rate of release over an extended period of time' (column 1, lines 17-19), in other words, a substantially zero order release rate.

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Conclusion

31. Claims 2-23 are rejected.

32. ***THIS ACTION IS MADE FINAL.***

A shortened statutory period for response to this action is set to expire 2 months from the mailing date of this action.

Extensions of time under 37 CFR 1.136(a) do not apply in reexamination proceedings. The provisions of 37 CFR 1.136 apply only to "an applicant" and not to parties in a reexamination proceeding. Further, in 35 U.S.C. 305 and in 37 CFR 1.550(a), it is required that reexamination proceedings "will be conducted with special dispatch within the Office."

Extensions of time in reexamination proceedings are provided for in 37 CFR 1.550(c). A request for extension of time must be filed on or before the day on which a response to this action is due, and it must be accompanied by the petition fee set forth in 37 CFR 1.17(g). The mere filing of a request will not effect any extension of time. An extension of time will be granted only for sufficient cause, and for a reasonable time specified.

The filing of a timely first response to this final rejection will be construed as including a request to extend the shortened statutory period for an additional month, which will be granted even if previous extensions have been granted. In no event, however, will the statutory period for response expire later than SIX MONTHS from the mailing date of the final action. See MPEP § 2265.

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Future Correspondence

33. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 571-272-0686. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Jones can be reached on 571-272-1535. The fax phone number for the organization where this application or proceeding is assigned is 571-273-9900.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

All correspondence relating to this ex parte reexamination proceeding should be directed:

By Mail to:	Mail Stop ex parte Reexam Central Reexamination Unit Office of Patent Legal Administration United States Patent & Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450
By FAX to:	571-273-9900 Central Reexamination Unit

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By Hand to: Customer Service Window
Randolph Building
401 Dulany St.
Alexandria, VA 22314

Evelyn Huang
Primary Examiner
Art Unit 3991

Conferee, Green

34. Based on the specific facts and circumstances of this proceeding, 37 CFR 1.530 is waived to the extent needed for entry of the 4/7/06 amendment, in order to further the statutorily requirement of 35 U.S.C. 305 that "All reexamination proceedings under this section...will be conducted with special dispatch within the Office."

Kenneth M. Schor
Senior Legal Advisor
Office of Patent Legal Administration

EXHIBIT B

Docket No.: ALZA-0141R (ARC02366)
Control No.: 90/007,772
Office Action Dated: June 20, 2006

MAIL STOP "*EX PARTE* REEXAM"

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: George V. Guittard, Francisco Jao, Susan M. Marks, David J. Kidney, Fernando E. Gumucio, Suneel Gupta, and Gayatri Sathyan
Patent No.: 6,919,092 B2
Issued: July 19, 2005
For: METHOD FOR THE MANAGEMENT OF INCONTINENCE

Confirmation No.: 3781
Examiner: Evelyn Huang
Technology Center Art Unit: 3991
Control No.: 90/007,772
Patentee: ALZA Corporation

CERTIFICATE OF FACSIMILE TRANSMISSION

DATE: August 21, 2006

I HEREBY CERTIFY THAT THIS PAPER IS BEING FACSIMILE TRANSMITTED TO THE PATENT AND TRADEMARK OFFICE TO FACSIMILE NUMBER 571-273-9900 ON THE DATE LISTED ABOVE.

Wendy A. Choi REG. NO. 36,697

Attention: Mail Stop "*Ex Parte* Reexam"
Central Reexamination Unit
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE PURSUANT TO 37 C.F.R. § 1.550(b)

In response to the Official Action in *Ex Parte* Reexamination dated **June 20, 2006**, reconsideration is respectfully requested in view of the amendments and/or remarks as indicated below:

- ☐ **Amendments to the Specification** begin on page of this paper.
- ☐ **Amendments to the Claims** are reflected in the listing of the claims that begins on page of this paper.
- ☐ **Amendments to the Drawings** begin on page of this paper and include an attached replacement sheet.
- ☒ **Remarks** begin on page 2 of this paper.

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REMARKS

Status of Claims

Claims 2 to 23 are subject to *ex parte* reexamination of US-B-6,919,092 ("the 092 Patent"). Claims 2 to 23 are pending. Claim 1 was previously cancelled. Claims 2, 3, 16, and 19 were previously amended. Claims 2 to 23 stand finally rejected. Patentee requests reconsideration of the rejections of claims 2 to 23.

Automatic Extension of Time

Patentee notes in accordance with M.P.E.P. § 2272 that this timely filed first response to the final rejection will automatically result in an extension of the shortened statutory period for an additional month (*i.e.*, through September 20, 2006).

Rejections

The following table summarizes the rejections maintained in the Second Office Action:

Claim	Rejection under 35 U.S.C.	Reference
3-23	§102(b)/§103(a)	Baichwal in view of Lukkari Cystrin insert
3-5, 8-10, 13-14, 16, 18-20, 23	§102(a)	Rantala
2	§102(a)	Baichwal
2	§102(e)	Baichwal
2	§103(a)	US-A-5,082,668 (Wong) PDR Robinson
2	§103(a)	US-A-5,330,766 (Morella) Robinson[1]

[1]Patentee notes that the Office maintained the rejection of claim 2 for alleged obviousness in view of the Morella patent, rather than for alleged anticipation, notwithstanding the oxybutynin-containing dosage form based on the patent that Mylan made in connection with the litigation involving US-B-6,124,355.

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All other rejections have been withdrawn. Patentee maintains its traversal of the remaining rejections, as explained more fully below, and request reconsideration of the claims in light of the amendments previously presented and following remarks.

Novelty Rejections over Rantala

Claims 3-5, 8-10, 13-14, 16, 18-20, and 23

Claims 3-5, 8-10, 13-14, 16, 18-20, and 23 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Example 3 and Table 4 of the Rantala application. Patentee maintains its traversal of the rejection because Example 3 does not disclose a maximum plasma oxybutynin concentration within the claimed range of about 0.28 ng/ml to about 0.45 ng/ml per mg. The Office notes that Example 3 refers to a C_{max} that it presumably divides by 10 mg to reach 0.213 ng/ml/mg. Although the Office concludes that 0.213 ng/ml/mg is "about" 0.28 ng/ml/mg oxybutynin (the lower limit recited in claim 3), the Office fails to identify any evidence supporting its apparent conclusion that those skilled in the art would deem 0.213 ng/ml/mg to be "about 0.28 ng/ml/mg" in spite of the fact that they differ by nearly 24% (*i.e.*, (0.28 – 0.213) ÷ 0.28). Accordingly, the rejection lacks evidentiary basis and should be withdrawn.

Novelty Rejections over Baichwal

Claim 2

Claim 2 stands rejected under 35 U.S.C. §§ 102(a) and (e) as allegedly anticipated by the tablet formulation of Example 3 of the Baichwal patent. Patentee maintains its traversal of the rejection because the Office has not demonstrated that this tablet formulation exhibits a zero order release rate for about 24 hours.

Contrary to the Office's position, plotting the release of drug that the Baichwal patent provides for Example 3 in Table 3 as a function of time does not produce a linear plot, much less a plot reflecting the claimed zero order release rate for about 24 hours. Although the Baichwal patent discloses controlled release delivery of oxybutynin generally, it does not

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disclose linear release for about 24 hours. Furthermore, Baichwal's experimental examples appear to release the vast majority of oxybutynin in 12 hours or less; there is no disclosure in the patent of linear, or zero-order, release for about 24 hours. That Example 3 of Baichwal may occasionally produce results that fall within claim 2 would be insufficient to establish anticipation.[2] *MEHL/Biophile Intern. Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999). Accordingly, the rejection for alleged anticipation is improper and should be withdrawn.

Claim 3-23

Claim 3-23 are rejected as allegedly anticipated by Example 3 of the Baichwal patent under 35 U.S.C. § 102(b), or alternatively, as obvious under 35 U.S.C. § 103(a). Patentee maintains its traversal of these rejections because the patent does not disclose the claimed maximum plasma oxybutynin concentration of about 0.28 ng/ml to about 0.45 ng/ml per mg.

As a first consideration, the Baichwal patent does not disclose that the oxybutynin tablets of Example 3 were actually administered to any patients in the prior art, much less that such administration produced the claimed range of maximum plasma oxybutynin concentrations. The Office appears to be aware of this deficiency, because it refers to two other references that are not prior art with respect to the instant claims (*i.e.*, the product insert for the Cystrin CR product and the Lukkari reference) in an attempt to demonstrate that Example 3 of the Baichwal patent constitutes an inherent anticipation of the instant claims. These references, however, fail to demonstrate any inherency because they discuss the concept of oxybutynin plasma concentration only in the context of specific test conditions that the Baichwal patent fails to so much as mention. As even the Office recognizes, the testing that is said to be disclosed in the Lukkari reference involved administration of the dosage form under fasting conditions, one hour before breakfast, or two hours after breakfast (First Office Action at page 9). Since the Baichwal patent does not even mention administering the dosage form disclosed in Example 3 under such conditions or any conditions, there is no basis for the Office's allegations of anticipation. *Continental Can Co.*

[2]See Cystrin Stipulation. *Alza Corp. v. Mylan Labs. Inc.*, Post-Trial Memorandum Opinion and Order, page 38 (Reference 264 on Form 1449 submitted on October 21, 2005).

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v. Monsanto Co., 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (to establish inherent anticipation, extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference"). Furthermore, even if administering the Baichwal dosage form will occasionally, but not invariably, result in the claimed maximum plasma oxybutynin concentration under certain conditions, then it is not sufficient to establish anticipation. *Glaxo Inc v. Novopharm Ltd.*, 52 F.3d 1043 (Fed. Cir. 1995) (prior art that falls within the patent claims even frequently, but not invariably, is not an inherent anticipation); *MEHL/Biophile Intern. Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999) ("occasional results are not inherent").

Accordingly, the rejection for alleged inherent anticipation or, alternatively, for alleged inherent obviousness is improper and should be withdrawn.

Obviousness Rejections under 35 U.S.C. § 103(a)

Wong in combination with PDR and Robinson

Claim 2 stands rejected under 35 U.S.C. § 103(a), as allegedly obvious over the Wong patent in combination with the PDR and Robinson references. Patentee maintains its traversal of the rejection because those of ordinary skill in the art would not have been motivated to combine the respective teachings of these references, or to prepare a dosage form that releases oxybutynin at a controlled and sustained, substantially zero order release rate for about 24 hours.

That motivation for the proposed combination would have been lacking is apparent from the Office's characterization of the cited references. Indeed, the respective teachings of the Robinson reference and Wong patent that the Office alleges to be relevant are plainly inconsistent. According to the Office, for example, the Robinson reference is relevant for its disclosure that oxybutynin possesses undesirable anticholinergic side effects that can be ***reduced*** through use of a modified release formulation of the drug (First Office Action at page 15; Second Office Action at page 15). The Wong patent, by contrast, is said to be relevant for its disclosure of a dosage form for drugs that are ***intended*** to act upon cholinergic receptors (First Office Action at page 15; Second Office Action at page 16). The Office does

not reconcile this inconsistency. In fact, there is simply no reason to believe that those of ordinary skill having knowledge a drug's undesirable side effects would have been motivated to incorporate the drug into a dosage form that they understood to have been designed to achieve that side effect.

Yet another reason for withdrawal of the rejection is that the conventional wisdom prior to the claimed inventions was that orally ingested, controlled-release products had to release drug in 8 to 12 hours, before the product reached the colon, because absorption through the colon was thought to be poor and variable (See, for example, Gupta and Robinson, *Treatise on Controlled Drug Delivery: Fundamentals, Optimization, Applications*, Marcel Dekker, Inc. 1992, 255-313, 268, copy enclosed). Thus, contrary to the Office's assertions, those of ordinary skill would not have been motivated to administer oxybutynin, as claimed, over a period of about 24 hours for the purpose of treating incontinence in a patient.

Based on the foregoing reasons, the rejection for alleged obviousness is thus improper, and should be withdrawn.

Morella in view of Robinson

Claim 2 stands rejected under 35 U.S.C. § 103(a), as allegedly obvious over the Morella patent in view of the Robinson reference. Patentee maintains its traversal of the rejection because there is no motivation to combine the references, but even if there were, the combination of the respective teachings of these references would not have produced any claimed invention.

First, there is no motivation to produce an oral dosage form of oxybutynin for treating incontinence in a patient that releases over about 24 hours because the skilled artisan would not have sought to deliver the drug via colonic absorption. As discussed above with respect to Wong, the conventional wisdom prior to the claimed inventions was that orally ingested, controlled-release products had to release drug in 8 to 12 hours, before the product reached the colon, because absorption through the colon was thought to be poor and variable (*Id.* at

268). Thus, contrary to the Office's assertions, those of ordinary skill would not have been motivated to administer oxybutynin, as claimed, over a period of about 24 hours.

Furthermore, neither the Morella patent nor Robinson reference discloses or suggests the claimed zero order release rate. Although the Office refers to Figure 5 of the Morella patent, the data points provided in the figure do not show a substantially zero order rate of release for about 24 hours. Notably, no data points are shown between 600 minutes (10 hours) and 1440 minutes (24 hours).

Thus, even if it would have been obvious to combine the respective teachings of the Morella patent and the Robinson reference (and Patentee does not concede that doing so would have been obvious), none of the resulting methods or dosage forms would have exhibited the claimed zero order release rate. Accordingly, the rejection under 35 U.S.C. § 103(a) is improper and should be withdrawn. *In re Payne*, 203 U.S.P.Q. 245, 255 (C.C.P.A. 1979) (references relied upon to support rejection under § 103 must place the claimed invention in the possession of the public).

Conclusions

Patentee respectfully requests reconsideration and withdrawal of the novelty and obviousness rejections in view of the previous amendments and foregoing remarks.

If the Examiner has any questions, the Examiner is invited to call the undersigned at (215) 568-3100.

Date: **August 21, 2006**

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